

REMARKS

This Amendment cancels claims 14-32 in favor of new claims 33-50. The new claims generally correspond to canceled claims 14-17 and 19-32. The trifluoroacetyl protecting group in new claim 33 is supported by Examples 1-4. One of ordinary skill in the art would understand "TAMRA" to mean "tetramethyl-6-carboxyrhodamine", as demonstrated by U.S. Patent No. 6,348,596 at Col. 55, lines 49-64. Claims 33-50 are pending.

Examiner Lewis is thanked for the courtesies extended to the undersigned during the telephonic interview held March 5, 2004. The Examiner Interview Summary Record accurately reflects the substance of the interview.

Examiner Lewis is also thanked for indicating the allowability of claim 32, if rewritten in independent form including all of the limitations of the base claim and any intervening claims. It is believed this Amendment places the entire application in condition for allowance for the reasons which follow.

This Amendment overcomes the objection to the claims. More particularly, claims 14-32 have been canceled in favor of new claims 33-50. Reconsideration and withdrawal of the objection to the claims are earnestly requested.

The 35 U.S.C. § 112, second paragraph, rejection of claim 18 for omitting essential elements is mooted by the cancellation of

that claim. Reconsideration and withdrawal of the indefiniteness rejection of claim 18 are earnestly requested.

This Amendment overcomes the 35 U.S.C. § 112, second paragraph, rejection of claims 14-31. More particularly, the new claims do not contain the informalities noted in the Official Action:

1. New claims 33-50 do not recite "temporary protecting group" or permanent protecting group".
2. New claims 33-50 do not recite the phrase "can be substituted".
3. New independent claim 33 specifies that "E' is bonded to Z at nitrogen in the pyrimidyl ring" and includes formulae showing this attachment, thereby overcoming the objection that the claims do not specify which hydrogen atom is substituted with E'.
4. New claim 39 identifies "TAMRA" as tetramethyl-6-carboxyrhodamine.

The remaining grounds for rejection are respectfully traversed. The mere fact that structures represented by G can be attached to linker E' at several points of attachment does not, by itself, render the claims indefinite. Section 112, second paragraph, requires patent claims to be sufficiently definite that one of ordinary skill in the art can tell, with a reasonable degree

of certainty, whether a particular compound is within or outside the scope of the claim. In this case, one of ordinary skill in the art would understand that any structure in which G is attached to linker E' is encompassed within the scope of the claims, regardless of their specific point of attachment. The Examiner's attention is directed to Ex parte Morton, 134 USPQ 407 (Bd. Pat. Appeals 1961) which held that a product claim is not indefinite merely because the exact position of a ring substituent and linkages between rings is not shown.

Reconsideration and withdrawal of the indefiniteness rejection of claims 14-31, as it may be applied to new claims 33-50, are earnestly requested.

The 35 U.S.C. § 112, first paragraph, rejection of claims 14-31, for lack of enablement is respectfully traversed. One of ordinary skill in the art would not be required to perform "undue experimentation" to synthesize the claimed labeling reactants by attaching G to the nucleotide via linker arm E'.

The applicants have discovered the Mitsunobu alkylation reaction can be used to react a 5'-O-protected nucleoside with an appropriate linker molecule E' (i.e., a primary alcohol having additional, protected functional groups, or alternatively, already reacted with G). The nucleoside is then converted to the

corresponding nucleotide in conventional manner to form a labeling reactant (Specification, page 15, lines 10-19).

Examination of the Wands factors demonstrates that one of ordinary skill in the art would not be required to perform undue experimentation to synthesize the claimed reactants by attaching G to the nucleotide via linker arm E':

1. **The Nature of the Invention** - The applicants have adapted a known organic synthesis reaction¹ to produce novel compounds for labelling of oligonucleotides. The starting materials are commercially available (Specification, page 15, lines 7-9). The use of known starting materials in a known reaction does not require "undue experimentation".
2. **The Amount of Guidance Presented** - The specification provides a detailed disclosure of the synthesis of oligonucleotide labeling reactants which enable preparation of ologinucleotides labeled with lanthanide III chelates. Two synthesis strategies are disclosed in the application:

¹The Mitsunobu reaction is an intermolecular dehydration reaction occurring between an alcohol and an acidic component upon treatment with diethyl azodicarboxylate and triphenyl phosphine under mild neutral conditions. The reaction exhibits stereospecificity and regional and functional selectivity. Hawley's Condensed Chemical Dictionary 789 (11th Ed. 1987).

- A. Synthesis of building blocks containing a protected functional group in their structure, their use in the synthesis of oligonucleotides bearing desired number of functional groups, and finally labeling of these functional groups with activated lanthanide III chelates.
- B. Synthesis of building blocks containing protected ligands in their structure, their use in the synthesis of oligonucleotide conjugates, and finally converting these conjugates to the corresponding lanthanide chelates after deprotection and treatment with a lanthanide salt.
Experimental details are provided for both synthesis strategies. One of ordinary skill in this art could prepare a desired reactant by employing the appropriate strategy without "undue experimentation".

3. **The Presence of Working Examples** - The specification contains 36 illustrative working examples, which include a detailed description of the instrumentation employed to characterize the synthesized compounds (page 20, lines 1-18). The weights and volumes of reagents, reaction times and temperatures for each example are set forth (See, for example, Example 1). Finally, the reaction strategies

employed in the Examples are illustrated in Schemes 2-11.

The presence of these numerous, detailed Examples is persuasive evidence that one of ordinary skill in the art would not be required to perform "undue experimentation" to synthesize a claimed labeling reactant.

4. **The Quantity of Experimentation Necessary** - The quantity of experimentation required to synthesize a particular compound is shown by the working examples in the application. One of ordinary skill in this art would consider such an organic synthesis *routine*, and not "undue" experimentation.
5. **The State of the Prior Art** - The prior art is highly developed. Synthetic oligonucleotides tethered to various ligands, and the introduction of multiple reporter groups to the nucleotide structure, are known. There are at least three known synthesis strategies for introduction of reporting groups. The use of linker arms is also known. See page 1, line 5 to page 5, line 8 of the specification. The existence of a highly developed state of the art is additional evidence that one of ordinary skill in the art would not be required to perform "undue experimentation" to synthesize one of the claimed labeling reactants.

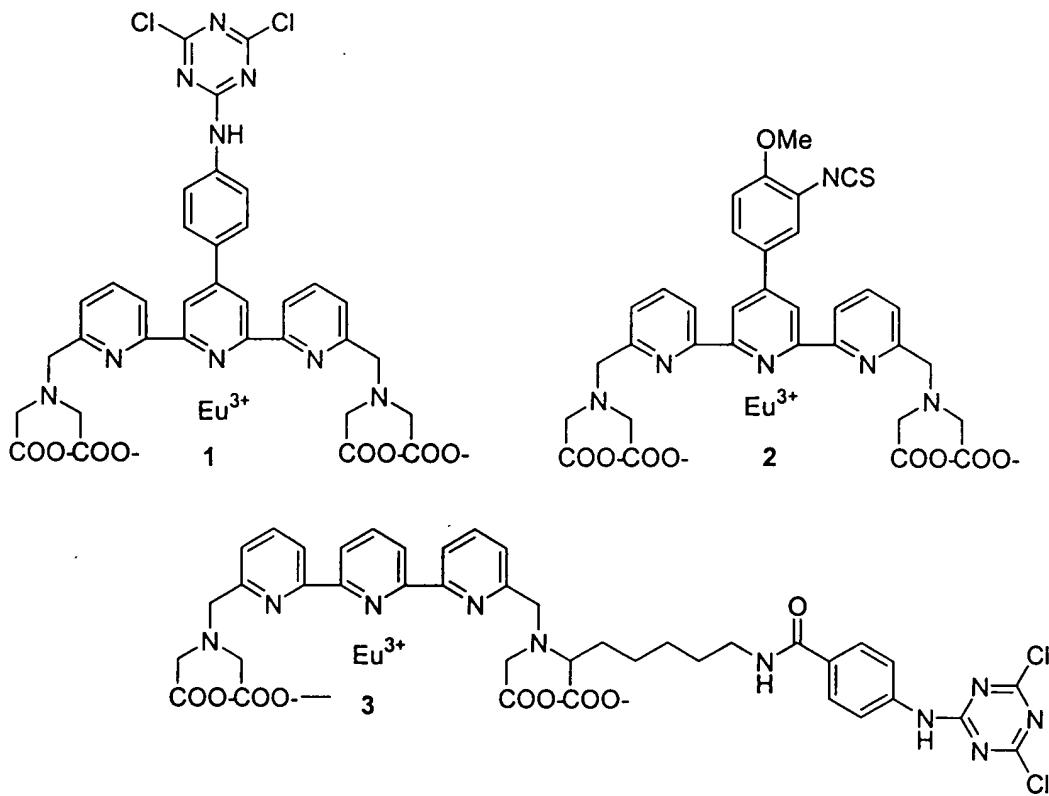
6. The Unpredictability of the Art - The nucleotide synthesis employed to make the claimed labeling reactants is not nearly as unpredictable as other arts such as genetic manipulation.

7. The Relative Skill of Those in the Art - The workers in this art possess a high level of skill, as reflected by the numerous articles published by workers in the field, and made of record in this application. A high level of skill is additional evidence that one of ordinary skill in the art would not be required to perform undue experimentation to synthesize one of the claimed labeling reactants.

One of ordinary skill in the art would understand from his background knowledge that E' (or Z if E' is not present) could replace any hydrogen atom in G. This is demonstrated by the following:

- A. U.S. Patent No. 6,080,839 discloses replacement of a hydrogen atom of the analogous bivalent aromatic atom (A in the '839 patent) with the analogous bridge (G in the '839 patent. See the abstract.
- B. Documents which disclose linkages of the bivalent aromatic atoms by replacement of different hydrogen atoms of bivalent structures which are equivalent

to G of the present application have been published prior to the filing of this application. Such structures, which can be found in the references submitted in the attached Supplemental Information Disclosure Statement, include the following:



8. **The Breadth of the Claims** - The applicants are entitled to claims sufficiently broad to encompass the numerous nucleotide derivatives which can be labeled according to the present invention. Similarly, the claims must be sufficiently broad to encompass the numerous ligands

which can be used to label the nucleotides. The precise point of attachment of G to E' is not critical to the claimed labeling reactant. In this regard, there are numerous alternatives to those specifically disclosed in the application, and it would unduly restrict the applicants' invention to limit the claimed invention to the subgenus defined in the Official Action.

Reconsideration and withdrawal of the 35 U.S.C. § 112, first paragraph, rejection of claims 14-31 are earnestly requested.

A Supplemental Information Disclosure Statement which cites additional references to show the high level of skill in this art and the existence of structures analogous to G is attached.

It is believed this application is in condition for allowance. Reconsideration and withdrawal of all rejections of claims 14-31, and issuance of a Notice of Allowance directed to claims 33-50, are earnestly requested. The Examiner is urged to telephone the undersigned should he believe any further action is required for allowance.

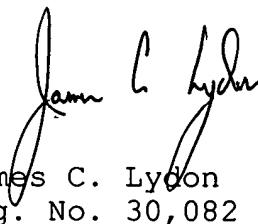
It is not believed any fee is required for entry and consideration of this Amendment. Nevertheless, the Commissioner is

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AMENDMENT

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authorized to charge our Deposit Account No. 50-1258 in the amount
of any such required fee.

Respectfully submitted,


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Enclosures:

Ex parte Morton, 134 USPQ 407 (Bd. Pat. Appeals 1961)
Hawley's Condensed Chemical Dictionary 789 (11th Ed. 1987)
Supplemental Information Disclosure Statement